REMARKS

Claims 21, 23, 25, 27, 29-36, 39-43 were pending in the application, with Claims 21, 40 and 41 being independent. Claims 21, 40, and 41 have been amended. Upon entry of these amendments, Claims 21, 23, 25, 27, 29-36, and 39-43 will be pending and under active consideration, with Claims 21, 40, and 41 being independent. The amendments are supported fully by the claims and/or specification as originally filed and, thus, do not represent new subject matter.

In particular, Claim 21 has been amended to recite said hepatocyte precursor cell is obtained by expanding isolated immature cells obtained from said subject to enrich for hepatocyte precursor cells, is genetically engineered *ex vivo* to be capable of treating said liver dysfunction, and is administered to the subject. Support for the amendment to Claim 21 may be found in the specification as originally filed (See, for example, page 2, lines 1-5 and page 2, lines 8-14).

Claim 40 has been amended to now recite a drug delivery system for delivering an expressed therapeutic polypeptide drug or protein drug to a subject having a liver dysfunction comprising genetically engineered hepatocyte precursor cells, wherein said hepatocyte precursor cells are obtained by expanding isolated immature cells obtained from said subject to enrich for hepatocyte precursor cells, genetically engineering said hepatocyte precursor to express a therapeutic polypeptide drug or protein drug, wherein the genetically engineered hepatocyte precursor cells express, as a result of said genetic engineering, said therapeutic polypeptide drug or protein drug in an amount effective to treat said liver dysfunction. Support for the amendment to Claim 40 may be found in the specification as originally filed (See, for example, page 2, lines

1-5 and page 2, lines 8-14).

Claims 41 has been amended so as to no longer recite the phrase "histocompatible normal" and "normal" as used in Claim 41.

Applicants wish to take this opportunity to thank the Examiner for the withdrawal of the rejection of Claims 21, 23, 25, 27, 29-36, and 39-40 under 35 U.S.C. § 112 which focused on the rejection of engrafted cells in a subject due to the immune reaction generated to cells comprising foreign antigens, and for the withdrawal of the rejection of Claims 21, 23, 25, 27, 29-36, and 39-40 under 35 U.S.C. § 112, first paragraph, which focused on the alleged failure of the instant disclosure to remedy the art recognized limitations for *in vivo* gene therapy protocols. Applicants also wish to thank the Examiner for the withdrawal of the rejection of Claims 21, 23, 25, 27, 29-36, and 39-40 under 35 U.S.C. § 112, first paragraph, which focused on the alleged new matter of the word "autologous," as well as for the withdrawal of the rejection of Claims 21, 23, 25, 27, 29-36, and 39-40 under 35 U.S.C. § 112, second paragraph.

Applicants respectfully request entry of the amendments and remarks made herein into the file history of the present invention. Reconsideration and withdrawal of the rejections set forth in the above-identified Final Office Action are respectfully requested.

I. Rejections Under 35 U.S.C. § 112, First Paragraph

At pages 1-8 of the Office Action, paper number 25, Claims 21, 23, 25, 27, 29-36, and 39-43 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Office

Action asserts that Claims 21, 23, 25, 27, 29-36, and 39-43, as amended, now only encompass a method of a method of *ex vivo* gene therapy wherein the hepatocyte precursor cells are first removed, genetically modified with a polynucleotide then returned to a subject for the treatment of any liver dysfunction with said genetically modified hepatocyte precursor cells. The Office Action alleges, further, that the dependent claims recite that the administration of said cells may be through injecting, transplanting, or grafting said cells into the subject, in particular the spleen, that a gene of interest can be inserted into the genome of the cell or maintained extrachromasomally, and recite a list of diseases for which said methodology could be used.

As alleged in the Office Action in the first paragraph on page 3, there are two main points of enablement are at issue; first, the ability of the disclosed composition of precursor cells to serve as hepatocyte precursor cells for treatment when placed into a subject, and second the lack of necessary guidance and skill in the art to provide treatment of a specific liver dysfunction by genetically engineering a hepatocyte precursor cell.

Finally, the Office Actions allege that the inclusion by Applicants of the phrase "a histocompatible normal hepatocyte precursor cell" constitutes "new matter." Applicants traverse respectfully.

A. The New Matter Rejection Should Be Withdrawn

The Office Action asserts, on page 8, that Claims 41 and 42 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was allegedly not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The Examiner has indicated that there is allegedly no support for the phrase 'a histocompatible

normal hepatocyte precursor cell'. Applicants traverse respectfully.

Without acquiescing in the propriety of the rejections, and solely to advance prosecution of the present application, Claim 41 has been amended so as to no longer recite the phrase "histocompatible normal" and the word "normal" as used in Claim 41.

Applicants request respectfully that, in view of the amendment to Claim 41, the aforementioned rejection of Claims 41 and 42 has been obviated. Accordingly, Applicants request respectfully that the new matter rejection of Claims 41 and 42 under 35 U.S.C. § 112, first paragraph, be withdrawn.

B. Rejections Of The Claims Based On Genetically Engineering A Hepatocyte Precursor Cell *Ex Vivo* Should Be Withdrawn

As noted above, the Office Action alleges, on pages 4-7, that Claims 21-23, 25, 27, 29-36, 39-43 encompass a method of treatment of liver dysfunction in a subject comprising administering a genetically engineered hepatocyte precursor to the subject, including a method of *ex vivo* gene therapy for the treatment of liver dysfunction with a genetically modified hepatocyte precursor cell, but that the specification is allegedly not enabling for these uses. The Office Action further alleges the specification only provides conditions and methods for isolating the precursor cells in the context of a composition of cells (see for example US Paten 6,146,889) and allegedly does not provide any guidance to isolate a population of hepatocyte precursor cells as a starting material as required by the instantly claimed methods or as present in the drug delivery system of claim 40.

Applicants wish to respectfully remind the Examiner that the Office Action expressly acknowledges that the specification as filed teaches the isolation of a composition of cells which

comprises hepatocyte precursor cells from the liver, and that culturing the precursor cells with liver stromal cells and an extracellular matrix one can effectively increase the number of said precursor cells. The specification as filed also points out with particularity that the hepatocyte precursor cells may be enriched so as to eliminate mature liver cells from the population by such procedures including, but not limited to, enzymatic digestion with pronase, DNase, and collagenase; centrifugal elutriation for cells which are smaller than mature hepatocytes; and freezing the cells in liquid nitrogen in the presence of 10% glycerol. (See, for example, specification at page 2, lines 8-13).

With respect to the Office Action's assertion that the starting cells of the method of Claim 21 and the starting cells of the drug delivery system of Claim 40 allegedly do not use the composition of cells claimed in U.S. Patent Nos. 6,146,889 and 5,789,246, without acquiescing in the propriety of the rejections, and solely to advance prosecution of the present application, Claim 21 has been amended so as to now more specifically point out and distinctly claim that which Applicants regard as their invention. In particular, Claim 21 has been amended to recite that the genetically engineered autologous hepatocyte precursor cell to be genetically engineered to be capable of treating said liver dysfunction is obtained from the subject by expanding isolated immature cells obtained from said subject to enrich for hepatocyte precursor cells, is genetically engineered *ex vivo* to be capable of treating said liver dysfunction, and is administered to the subject. Support for the amendment to Claim 21 may be found in the specification as originally filed (See, for example, page 2, lines 1-5 and page 2, lines 8-14).

Applicants respectfully submit that, in view of the amendment to Claim 21, such *ex vivo* genetic engineering of an autologous hepatocyte precursor cell obtained from a subject by expanding isolated immature cells obtained from said subject to enrich for hepatocyte precursor

cells is now enabled inasmuch as claims to such hepatocyte precursor genetically engineered cells have been allowed in two parent cases of the present application. In particular, the present application is a continuation of 09/115,920, now U.S. Patent No. 6,146,889, which is a continuation of 08/751,546, now U.S. Patent No. 5,789,246. Applicants respectfully submit that Claim 4 of U.S. Patent No. 6,146,889 recites "genetically engineered hepatocyte precursor cells obtained by genetically engineering expanded hepatocytes precursor cells derived from culturing immature animal cells that contain at least a population of hepatocyte precursor cells capable of differentiating into hepatocytes." Applicants also respectfully submit that Claim 2 of U.S. Patent No. 5,789,246 recites "genetically engineered hepatocyte precursor cells obtained by culturing ... hepatocyte precursor cells capable of differentiating into hepatocytes ... to provide expanded hepatocyte precursor cells and genetically engineering the expanded hepatocyte precursor cells."

Similarly, Applicants have amended Claim 40 so as to now recite a drug delivery system for delivering an expressed therapeutic polypeptide drug or protein drug to a subject having a liver dysfunction comprising genetically engineered hepatocyte precursor cells, wherein said hepatocyte precursor cells are obtained by expanding isolated immature cells obtained from said subject to enrich for hepatocyte precursor cells, genetically engineering said hepatocyte precursor to express a therapeutic polypeptide drug or protein drug, wherein the genetically engineered hepatocyte precursor cells express, as a result of said genetic engineering, said therapeutic polypeptide drug or protein drug in an amount effective to treat said liver dysfunction. Applicants respectfully submit that in view of the amendment to Claim 40, the rejection of Claim 40 as being non-enabled has been overcome and withdrawal thereof is respectfully requested.

Accordingly, Applicants submit respectfully that, in view of the amendments to Claims

21 and 40, the rejection of Claims 21, 23, 25, 27, 29-36, 39-43 based on the alleged lack of the ability of the disclosed composition of precursor cells to serve as hepatocyte precursor cells for use in the methods and drug delivery system of the invention has been overcome and withdrawal thereof is respectfully requested.

With respect to the allegation, made in the Office Action on page 4, that the specification as filed does not provide any substantive guidance for demonstrating that isolated hepatocyte precursor cells will maintain a precursor-like state or will differentiate into mature hepatocytes *in vitro* or *in vivo*, Applicants submit respectfully once again that, not only does the specification as filed provide literal support for the contention that hepatic precursors may maintain a precursor-like state or differentiate into mature hepatocytes under various conditions, but that such contention is presumptively true as confirmed on the record. Respectfully, Applicants turn Examiner's attention to page 13, bottom, of paper number 7, Final Office Action mailed December 4, 2000, which recites that the capability of a hepatocyte precursor cell to differentiate into a hepatocyte "is a necessary and defining characteristic of a hepatocyte precursor cell."

Moreover, Applicants submit respectfully that literal support for such cell cultures of hepatocyte precursors maintaining a precursor-like state or being capable of differentiation into mature hepatocytes under various conditions is replete within the entirety of the specification as filed; see, for example, pages 6-7. Furthermore, allowed claims in the patents issued from parent applications of the present application are directed to cell cultures of hepatic precursor cells that have the capability to differentiate into mature hepatocytes (see, for example, Claim 1 of U.S. Patent No. 5,789,246); therefore, such cell culture is presumptively enabled in the present application. Accordingly, Applicants submit respectfully that U.S. Patent No. 5,789,246, by demonstrating that such cell cultures of hepatic precursor cells have the capability to differentiate

into mature hepatocytes, effectively rebuts the *prima facie* case of lack of enablement.

Accordingly, Applicants submit respectfully that the rejection based on alleged lack of enablement for demonstrating that isolated hepatocyte precursor cells will maintain a precursor like state or will differentiate into mature hepatocytes has been overcome and withdrawal thereof is respectfully requested

CONCLUSION

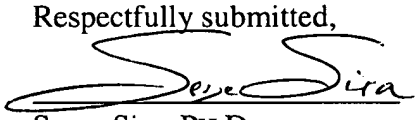
Applicants submit that the application is in condition for allowance. Favorable reconsideration, withdrawal of the rejections set forth in the above-noted Final Office Action, and an early Notice of Allowance are requested.

Applicants' undersigned attorney may be reached in our Washington, D.C. office by telephone at (202) 625-3500. All correspondence should be directed to our address given below.

AUTHORIZATION

Applicants believe there is no additional fee due in connection with this filing. However, to the extent required, the Commissioner is hereby authorized to charge any fees due in connection with this filing to Deposit Account 50-1710 or credit any overpayment to same.

Respectfully submitted,



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